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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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10 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATION OF CELL PHENOTYPE BY INHIBITORY RNA

(57) Abstract: We describe a method to inhibit cell division of hyperproliferative cells, typically cancer cells, by introducing inhibitory RNA (RNAi) into said cells to ablate mRNAs that encode polypeptides involved in cellular processes and including RNAi molecules and vectors including transcription cassettes encoding said RNAi molecules. By application of said RNAi molecules to cancers *in vivo* it is possible to effect a treatment whereby the cancer cells are killed or otherwise eliminated.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/11 A61K31/713 A61K48/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/16620 A (ANDREWS PETER ; WALSH JAMES (GB); GOKHALE PAUL (GB); UNIV SHEFFIELD (G) 28 February 2002 (2002-02-28) the whole document	5-14
X	WO 03/012082 A (ANDREWS PETER ; AXORDIA LTD (GB); WALSH JAMES (GB); GOKHALE PAUL (GB)) 13 February 2003 (2003-02-13)	5-14
Y	the whole document	1-4, 15-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 2004	12. 01. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PAN GUANG JIN ET AL: "Stem cell pluripotency and transcription factor Oct4." CELL RESEARCH, [Online] vol. 12, no. 5-6, December 2002 (2002-12), pages 321-329, XP002295356 ISSN: 1001-0602 Retrieved from the Internet: URL:www.cell-research.com/20024/0256-pdq.html> the whole document	1-4, 17-25
Y	WO 02/08388 A (KRUIJER WIEBE ; UNIV GRONINGEN (NL); FORNIX BIOSCIENCES N V (NL)) 31 January 2002 (2002-01-31) the whole document	15,16
X	DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; March 2003 (2003-03), MENG GUO-LIANG ET AL: "[RNA interference in three ES cell lines from different mouse strains]" XP002295358 Database accession no. NLM12621548 abstract & SHENG WU HUA XUE YU SHENG WU WU LI XUE BAO ACTA BIOCHIMICA ET BIOPHYSICA SINICA. MAR 2003, vol. 35, no. 3, March 2003 (2003-03), pages 238-246, ISSN: 0582-9879	5,8-11, 14
A	WO 00/22136 A (CANJI INC) 20 April 2000 (2000-04-20) cited in the application the whole document	14-16
A	DRAPER J S ET AL: "SURFACE ANTIGENS OF HUMAN EMBRYONIC STEM CELLS: CHANGES UPON DIFFERENTIATION IN CULTURE" JOURNAL OF ANATOMY, vol. 200, no. PART 3, March 2002 (2002-03), pages 249-258, XP001152867 ISSN: 0021-8782 cited in the application	
A	STEWART C L: "Oct-4, scene 1: the drama of mouse development" NATURE GENETICS, vol. 24, no. 4, April 2000 (2000-04), pages 328-330, XP002155943 ISSN: 1061-4036	

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INTERNATIONAL SEARCH REPORT

PCT/GB2004/001374

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANDREWS PETER W: "From teratocarcinomas to embryonic stem cells" PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON B BIOLOGICAL SCIENCES, vol. 357, no. 1420, 29 April 2002 (2002-04-29), pages 405-417, XP002295357 ISSN: 0962-8436 cited in the application	
P,A	WO 03/080816 A (ANDREWS PETER ; DRAPER JON (GB); UNIV SHEFFIELD (GB)) 2 October 2003 (2003-10-02) cited in the application the whole document	14-16
P,X	VELKEY J MATTHEW ET AL: "Oct4 RNA interference induces trophectoderm differentiation in mouse embryonic stem cells." GENESIS THE JOURNAL OF GENETICS AND DEVELOPMENT, vol. 37, no. 1, September 2003 (2003-09), pages 18-24, XP008035096 ISSN: 1526-954X the whole document	5-11,13, 14
T	MATIN, M. ET AL.: "Specific knockdown of Oct4 and beta2-microglobulin expression by RNA interference in human embryonic stem cells and embryonic carcinoma cells" STEM CELLS, vol. 22, no. 5, September 2004 (2004-09), pages 659-668, XP008035005	

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   - [X] a sequence listing
   - [ ] table(s) related to the sequence listing

   b. format of material

   - [X] In written format
   - [X] In computer readable form

   c. time of filing/furnishing

   - [ ] contained in the international application as filed
   - [ ] filed together with the international application in computer readable form
   - [X] furnished subsequently to this Authority for the purpose of search

2. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-4 and 17-21 encompass or are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-25 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1.: Claims 1-25 (all partially)

An RNAi molecule targeting Oct4 (fig.9); nucleic acids comprising and expressing it, and their use in the inhibition of cancer cell division.

Inventions 2. to 8.: Claims 1-25 (all partially)

As for invention 1., but concerning respectively the target nucleic acid sequences outlined in figures 10 to 16.

INTERNATIONAL SEARCH REPORT

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0216620 A	28-02-2002	AU 8416001 A	04-03-2002
		CA 2456008 A1	28-02-2002
		CN 1449448 T	15-10-2003
		EP 1309706 A2	14-05-2003
		WO 0216620 A2	28-02-2002
		JP 2004522414 T	29-07-2004
		US 2004053869 A1	18-03-2004
WO 03012082 A	13-02-2003	WO 03012082 A2	13-02-2003
WO 0208388 A	31-01-2002	EP 1176189 A1	30-01-2002
		AU 8631501 A	05-02-2002
		CA 2416682 A1	31-01-2002
		EP 1301590 A2	16-04-2003
		WO 0208388 A2	31-01-2002
		US 2003219866 A1	27-11-2003
WO 0022136 A	20-04-2000	AU 1092500 A	01-05-2000
		CA 2345211 A1	20-04-2000
		EP 1121442 A2	08-08-2001
		JP 2002527455 T	27-08-2002
		WO 0022136 A2	20-04-2000
WO 03080816 A	02-10-2003	EP 1485479 A2	15-12-2004
		WO 03080816 A2	02-10-2003